Efficacy Evaluation in Acne Clinical Trials

An Outline

I. Re-visit choice of the primary endpoint for analysis: change score, relative change and lesion counts (statistical viewpoint).

II. Statistical analysis for efficacy evaluation:
   a) Analysis units: original vs. transformed data
   b) Analysis methods

III. Gain in power using subject's repeated assessments in lieu of the final assessment.

IV. Do efficacy findings (whether based on change, counts or IGE) vary by baseline severity?

I. Re-visit choice of primary endpoint for analysis: change score, relative change and lesion counts (statistical viewpoint):

Efficacy assessment for acne lesions (Inflammatory, Non-inflammatory or Total lesions) can be carried out by analysis of:

- ✓ final lesion counts
- ✓ change score or relative change score (percent change)

Pros and Cons of analysis based on change score:

(a) Easy to interpret and analyze

(b) Attempt to remove the influence of baseline counts on the final counts but may fail since change is negatively correlated with final counts.

(c) Converting baseline and final lesions counts to relative change score may result in highly skewed (asymmetrical) distribution, which violate most parametric statistical tests.

(Figures 1-3: plots of infl., non-infl and total lesion counts, their change and relative changes by study visits, Drug X, Study 1)

(Figures 4-6: plots of infl., non-infl and total lesion counts, their change and relative changes

by study visits, Drug Y, Study 2)

II. Statistical analysis for efficacy evaluation:

a) Analysis units: original vs. transformed data: (pros and cons)

b) Analysis methods for endpoints (change or final counts):

(i) Simple comparisons of primary endpoints:
(ii) ANOVA model with treatment, center and their interaction:
(iii) ANCOVA with baseline lesion counts as covariates to account for possible baseline imbalance or regression toward the mean.

III. Gain in power using subject's repeated assessments in lieu of final assessment.

As successive assessments of a subject lesion counts over the course of the trial are expected to be correlated, one expects that use of these repeated assessments would increase the power for detecting treatment difference. We compare the efficacy based on repeated measurements (GLM, MIXED, MANOVA) approach against that based on the final assessment.

(Table 1: Comparison of efficacy results of various statistical approaches, Drug X, Study 1)
(Table 2: Comparison of efficacy results of various statistical approaches, Drug Y, Study 2)

IV. Do efficacy findings (whether based on change, counts or IGE) vary by baseline severity?

To find out whether efficacy results varies by baseline lesion counts:

- ✓ Divide baseline lesion counts (infl., non-infl, and total) to categories (say 4) with roughly equal number of subjects in each category.
- ✓ compares efficacy results across the categories

(Figures 7-9: Plots of Infl., non-infl, & total lesion counts, their changes and relative changes by baseline category, Drug X, Study 1)

(Figures 10-12: Plots of Infl. non-infl, & total lesion counts, their change and relative changes by baseline category, Drug Y, Study 2)

(Table 3-4: Comparison of efficacy results based on lesion counts & IGE by baseline category, Drug X, Study 1)

(Table 5-6: Comparison of efficacy results based on lesion counts & IGE by baseline category, Drug Y, Study 2)

Table 1: Comparison of efficacy results of various statistical methods (Drug X, Study 1)

	Infl. lesions		Non-Infl. lesions		Total lesions	
	Data	Ranks	Data	Ranks	Data	Ranks
Counts	(18.4, 20.6)*		(37.4, 46.7)*		(55.8, 67.2)*	
MANOVA	0.306	0.069	<0.001	<0.001	<0.001	<0.001
GLM (R)	0.316	0.219	0.010	0.006	0.0129	0.003
Week 12	0.130	0.044	0.002	<0.001	0.002	<0.001
Week 8	0.308	0.222	0.003	0.002	0.005	<0.001
Week 4	0.834	0.917	0.270	0.418	0.325	0.293
Change	(9.2, 6.4)*		(26.0, 15.5)*		(35.1, 21.9)*	
MANOVA	0.176	0.158	<0.001	<0.001	<0.001	<0.001
GLM (R)	0.081	0.134	<0.001	<0.001	<0.001	<0.001
Week 12	0.031	0.040	<0.001	<0.001	<0.001	<0.001
Week 8	0.116	0.132	<0.001	0.001	<0.001	<0.001
Week 4	0.429	0.789	0.020	0.021	0.027	0.030
% Change	(32.1, 21.4)*		(41.1, 24.8)*		(38.8, 24.8)*	
MANOVA	0.067	0.046	<0.001	<0.001	<0.001	<0.001
GLM (R)	0.079	0.0614	<0.001	<0.001	<0.001	<0.001
Week 12	0.012	0.008	<0.001	<0.001	<0.001	<0.001
Week 8	0.201	0.108	<0.001	0.001	<0.001	<0.001
Week 4	0.498	0.712	0.050	0.037	0.023	0.034

(active, vehicle)*

Table 2: Comparison of efficacy results of various statistical methods (Drug Y, Study 2)

	Infl. lesions		Non-Infl. lesions		Total lesions	
	Data	**Ranks**	**Data**	**Ranks**	**Data**	**Ranks**
Counts	(13.7, 16.2)*		(43.6, 49.2)*		(57.3, 65.3)*	
GLM (R)	0.020	0.031	0.415	0.120	0.211	0.023
Cycle 6	0.020	0.018	0.294	0.071	0.161	0.022
Cycle 5	0.031	0.024	0.636	0.231	0.327	0.072
Cycle 4	0.160	0.375	0.803	0.099	0.561	0.098
ANCOVA(R)	0.015	0.016	0.072	0.030	0.021	0.001
ANCOVA	0.014	0.032	0.044	0.017	0.015	< 0.001
Simple test	0.068	0.035	0.428	0.176	0.288	0.077
Change	(8.1, 5.7)*		(6.6, -2.4)*		(14.7, 3.3)*	
GLM (R)	0.037	0.017	0.043	0.008	0.013	0.001
Cycle 6	0.060	0.036	0.027	0.001	0.010	< 0.001
Cycle 5	0.016	0.007	0.204	0.024	0.063	0.002
Cycle 4	0.117	0.124	0.240	0.014	0.118	0.001
ANCOVA(R)	0.015	0.009	0.072	0.003	0.021	< 0.001
ANCOVA	0.014	0.023	0.044	< 0.001	0.015	< 0.001
Simple test	0.093	0.050	0.055	0.004	0.028	< 0.001
% Change	(31.0, 22.0)*		(13.2, -5.2)*		(22.6, 8.5)*	
GLM (R)	0.076	0.009	0.035	0.005	0.003	< 0.001
Cycle 6	0.097	0.017	0.021	0.005	0.002	< 0.001
Cycle 5	0.078	0.010	0.078	0.020	0.010	0.004
Cycle 4	0.249	0.188	0.039	0.012	0.021	0.004
ANCOVA(R)	0.074	0.008	0.061	0.005	0.005	< 0.001
ANCOVA	0.096	0.016	0.037	0.004	0.004	< 0.001
Simple test	0.102	0.020	0.040	0.013	0.010	< 0.001

(active, vehicle)*

Table 3: Comparison of efficacy results by baseline category (Drug X, Study 1)

Lesion Type	Data	Baseline Category, mean (s.d.)			
		1	2	3	4
Inflammatory	**Counts**				
	Active	13.3 (9.8)	17.0 (10.3)	19.4 (17.8)	23.2 (18.4)
	Placebo	13.2 (10.0)	20.0 (10.5)	22.9 (15.2)	26.8 (21.0)
	Change				
	Active	6.2 (9.2)	7.6 (9.6)	8.3 (14.4)	13.6 (19.0)
	Placebo	4.3 (8.8)	6.0 (11.2)	6.9 (13.5)	8.9 (15.7)
	%Change				
	Active	30.9 (45.3)	28.4 (43.9)	32.2 (40.5)	35.9 (42.5)
	Placebo	24.4 (51.7)	18.4 (48.9)	17.7 (67.8)	26.8 (37.0)
Non-inflammatory	**Counts**				
	Active	18.1 (11.7)	25.7 (15.9)	41.3 (23.7)	59.7 (38.1)
	Placebo	23.5 (12.1)	36.7 (18.4)	47.0 (23.5)	85.6 (43.7)
	Change				
	Active	14.7 (12.4)	19.1 (16.9)	24.1 (23.4)	42.5 (34.1)
	Placebo	10.9 (12.1)	7.8 (17.9)	17.5 (20.8)	26.6 (35.6)
	%Change				
	Active	44.0 (35.3)	41.3 (36.9)	35.8 (35.8)	42.6 (30.9)
	Placebo	31.2 (34.5)	17.0 (38.2)	27.2 (34.8)	21.9 (34.4)
Total	**Counts**				
	Active	31.4 (17.7)	42.7 (21.6)	60.8 (33.3)	82.9 (47.1)
	Placebo	36.7 (16.3)	56.6 (21.7)	69.8 (27.8)	112.5 (50.6)
	Change				
	Active	20.9 (17.1)	26.7 (21.8)	32.3 (31.0)	56.1 (45.7)
	Placebo	15.3 (15.8)	13.9 (22.6)	24.4 (25.9)	35.4 (45.1)
	%Change				
	Active	40.2 (32.0)	38.3 (30.5)	35.3 (33.0)	40.8 (30.6)
	Placebo	29.4 (30.7)	19.1 (32.0)	26.2 (28.2)	23.5 (30.2)

Table 4: Comparison of efficacy results based on IGE by baseline category (Drug X, Study 1)

Treatment	Baseline Category				Overall
	1	2	3	4	
Active	18/51 (35%)	11/53 (21%)	4/46 (9%)	7/68 (10%)	40/218 (18%)
Placebo	13/49 (27%)	6/56 (11%)	6/61 (10%)	0/52 (0%)	25/218 (11%)

Table 5: Comparison of efficacy results by baseline category (Drug Y, Study 2)

Lesion Type	Data	Baseline Category, mean (s.d.)			
		1	2	3	4
Inflammatory	**Counts**				
	Active	9.55 (8.6)	11.76 (8.9)	14.49 (9.4)	18.88(17.1)
	Placebo	10.17 (5.9)	12.03 (8.0)	17.37 (9.7)	24.36 (23.5)
	Change				
	Active	1.90 (8.9)	3.94 (8.9)	7.42 (9.2)	19.71 (17.7)
	Placebo	1.46 (5.9)	3.51 (8.3)	4.22 (9.6)	13.91 (23.1)
	%Change				
	Active	14.83 (76.9)	25.05 (56.9)	33.93 (42.2)	49.87 (36.7)
	Placebo	12.30 (50.0)	21.44 (54.9)	19.42 (44.1)	36.19 (52.4)
Non-inflammatory	**Counts**				
	Active	10.31 (8.2)	17.66 (10.6)	38.86 (37.1)	110.7 (105.3)
	Placebo	13.17 (13.7)	22.47 (20.6)	44.02 (40.8)	112.3 (96.6)
	Change				
	Active	0.98 (8.2)	4.57 (10.0)	7.33 (37.0)	13.70 (86.8)
	Placebo	-1.76 (13.5)	-0.51 (21.1)	0.24 (38.7)	-7.10 (71.7)
	%Change				
	Active	5.44 (80.3)	20.19 (46.4)	14.80 (89.4)	11.79 (69.5)
	Placebo	-17.7 (126.7)	-6.7 (109.4)	3.11 (85.5)	0.31 (56.8)
Total	**Counts**				
	Active	21.70 (12.4)	33.52 (23.4)	50.22 (37.8)	127.6 (117.1)
	Placebo	25.84 (20.3)	35.75 (18.9)	60.00 (31.4)	139.5 (105.5)
	Change				
	Active	5.35 (12.4)	9.37 (22.0)	19.48 (36.9)	25.05 (95.2)
	Placebo	0.76 (19.9)	7.48 (17.9)	11.20 (30.5)	-5.62 (84.2)
	%Change				
	Active	19.20 (45.1)	23.00 (47.9)	28.25 (50.4)	19.48 (57.9)
	Placebo	2.76 (67.8)	17.71 (40.3)	15.51 (42.4)	-0.84 (60.9)

Table 6: Comparison of efficacy results based on IGE by baseline category (Drug Y, Study 2)

Treatment	Baseline Category				Overall
	1	2	3	4	
Active	28/43 (65%)	25/51 (49%)	21/46 (46%)	15/44 (34%)	89/184 (48%)
Placebo	28/49 (57%)	17/42 (40%)	12/46 (26%)	12/47 (26%)	69/184 (38%